

Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

Biochimica et Biophysica Acta 1695 (2004) 1–2

<http://www.elsevier.com/locate/bba>

Editorial

Death gives birth to life: the essential role of the ubiquitin–proteasome system in biology

Life depends on a multitude of physical and chemical reactions, which proceed in single cells and multicellular organisms. Life becomes only possible when all these reactions are precisely controlled in time and space. Chaos is hostile as can be easily seen in our daily life. The “workers” making all reactions possible in cells are the proteins and, interestingly, they are the “controlling officers” at the same time. Life can only go on when cells and organisms are able to respond to external signals and inbuilt internal programs. Otherwise disease and death are the consequence. Thus, the proteins must be able to alter the cellular reactions in a way, which adapts cells to the new environment or the altered internal program. This requests either change of the proteins’ activity brought about by conformational alterations or changes in their concentration. One mechanism to achieve the goal of conformational change upon an incoming signal rests in the proteins’ binding of a chemical product generated in the cell. Another very “popular” tool to change a protein’s conformation and thus its cellular activity rests in its phosphorylation–dephosphorylation. In many instances, these regulatory devices suffice. They have, however, one drawback; as do all reactions they underlie the rule of the chemical equilibrium: The status of activity or inactivity of a protein is controlled by the reactants and products. Thus, complete shutoff of a protein’s activity will only be achieved by an infinite concentration of the inactivating reactant. This cannot be achieved in cells. How to reach the goal of complete shutoff? Complete degradation of the controlled protein is the solution. For many years, however, the degradation of proteins as regulatory tool was inconceivable for researchers due to economics: It was implausible that the cell would destroy its proteins, which it had synthesized at the expense of a huge amount of energy. Only degradation of protein waste in the gut of the cell, the lysosome, seemed reasonable. It was completely neglected that—like in normal life—high sophistication and quality is very costly. Thus, cells do not care about costs (energy) when they require precise regulation of their reactions, a fact which made evolution

of higher organisms, as we are, possible. The discovery of the 2004 Noble Prize winners in Chemistry, Avram Herskko, Aaron Ciechanover and Irwin Rose, in the late 1970s and early 1980s of the last century, that the 76-amino-acid protein ubiquitin is linked to proteins to address them for degradation remained rather unrecognized for many years. The elucidation of the essential pieces of the ubiquitination machinery and the discovery of first in vivo functions were crucial in the acceptance of ubiquitin-linked degradation of proteins as a mechanism of cell regulation. The final breakthrough was reached when a since long known “multicatalytic-multifunctional protease”—now termed proteasome—could be linked in vivo to the degradation of the ubiquitinated proteins. Since then, selective proteolysis via the ubiquitin–proteasome system (UPS) became a hot topic in biological sciences. The “kiss of death”, the polyubiquitination of selected proteins, leads to their recognition by the guillotine-like machinery—the proteasome, which finally executes the “death sentence” degrading them into peptide pieces. Only death of the proteins, which are destined to degradation on the basis of incoming signals or intracellular programs, makes life possible: Cell cycle control and apoptosis, cell metabolism, signal transduction, DNA repair, organismal development, immune response and, last but not least, protein garbage disposal are biological processes, which are crucially dependent on the precise function of the ubiquitin–proteasome system. Malfunctioning of components of the system leads to severe human diseases, among them neurological disorders, inflammatory processes and cancer. The ubiquitin–proteasome system is therefore central for pharmacological intervention to treat diseases. Most interestingly, a proteasome inhibitor, bortezomib (Velcade™), has been found to induce apoptosis in cancer cells and is currently being evaluated in multiple phase I–III clinical trials to treat multiple myeloma, NHL and solid tumor cancers. Intervention at the different levels of the ubiquitin activation and conjugation machinery will most likely be highly promising for future drug discovery.

Ubiquitin has even more surprises in store: Cells exploit its proteinaceous character and its ability to form variable structures when linked to each other at different locations in a variety of different ways to suit other regulatory purposes than proteasomal degradation of proteins. The discovery of ubiquitin-like proteins, their use in protein modification and their integration into ubiquitin-signalled regulatory processes add a fascinating additional layer of complexity to cellular regulation mechanisms. The Nobel Prize winners have opened a door into a previously closed room which now confronts their followers with many more doors to open.

Dieter H. Wolf*

Wolfgang Hilt

University of Stuttgart, Institute for Biochemistry,

Pfaffenwaldring 55, 70569 Stuttgart, Germany

E-mail address: dieter.wolf@ibc.uni-stuttgart.de.

*Corresponding author. Tel.: +49 711 685 4390;

fax: +49 711 685 4392.

Thomas Sommer

Max-Delbrück-Centrum für Molekulare Medizin,

Robert-Rössle-Str. 10, 13092 Berlin, Germany